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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/289,576	04/09/1999	RICHARD C. ALLEN	398802000600	8803

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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/289,576	ALLEN ET AL.	
	Examiner	Art Unit	
	Anne Baker	1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-17 and 19-40* is/are pending in the application.

4a) Of the above claim(s) *19-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-17 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment filed November 5, 2001 (Paper No. 15) has been entered. Claims 1, 4-6, 8, 11, 15, 16, and 37-39 have been amended. Claims 7, 18, and 41-43 have been cancelled.

Claims 1-6, 8-17, 19-40 remain pending in the instant application.

Claims 19-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Thus, Claims 1-6, 8-17, and 37-40 are examined herein.

This application contains claims 19-36 drawn to an invention nonelected without traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-17, and 38, stand rejected and Claims 37, 39, and 40 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action of Paper No.

12 (mailed 5/7/01), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for providing dopamine or a dopamine precursor to a subject with schizophrenia, a pharmaceutical composition comprising therapeutic cells and Sertoli cells, a pharmaceutical composition comprising therapeutic cells, protective cells, and support cells, and a kit comprising therapeutic cells, protective cells, support cells, and a support matrix.

Claims 37, 39, and 40 have been amended so that the compositions now being claimed are structurally different from those originally claimed.

In the paragraph bridging pages 5-6 of the response, Applicants argue that the art indicates that dopamine deficits in the prefrontal cortex have been detected in subjects with schizophrenia and that these deficits may be implicated in the negative symptoms of schizophrenia. In the previous Office Action (Paper No. 12, mailed 5/7/01), at pages 3-4, the Examiner pointed out that Seibyl et al. (U.S. Patent No. 5,447,948), pointing to the work of Weinberger and others, stated that "mesofrontal dopamine deficits may be implicated in negative schizophrenic symptoms" (Column 1, lines 44-46). However, it is a huge leap to use this statement as the sole evidence to support the notion that a dopamine replenishment strategy, directed to a specific region of the brain, will be effective in treating the negative symptoms of schizophrenia. Applicants have offered no other evidence to support the notion that a dopamine replenishment strategy will be effective in treating the negative symptoms of schizophrenia. As discussed in the previous Office Action at page 3, paragraph 1, the etiology of schizophrenia is not well-understood and treatment of the disease is generally limited to treating specific symptoms (National Institute of Mental Health, Schizophrenia, 1999, pp. 6-7). Although dopamine **antagonists** have been shown to be effective

in treating the symptoms of schizophrenia, the effect of dopamine **replenishment** in specific areas of the brain is not known. The specification fails to provide an enabling disclosure for the claimed method for treating negative symptoms of schizophrenia in a subject because the specification does not adequately teach how to use the claimed method to produce the intended effect. In Example 1, the specification discloses that Vervet monkeys were administered PCP by intramuscular injection and subsequently were given human RPE cells adhered to crosslinked gelatin microspheres. However, the specification does not disclose what effect these cells had on the negative symptoms provoked by PCP injection. Thus, the specification and Applicants' arguments presented here, which rely solely on the statements of Seibyl et al. (1995), fail to convincingly demonstrate that a dopamine replenishment strategy, directed to the prefrontal cortex of the brain, would be expected to result in treatment of the negative symptoms of schizophrenia. Given that the etiology of schizophrenia is not well-understood, the effect of specific treatment modalities (such as dopamine replenishment) that have not been tested would be considered unpredictable. Moreover, given that the effects of *ex vivo* gene therapy and cell-based therapies are unpredictable, as discussed at pages 3-6 of the previous Office Action (Paper No. 12, mailed 5/7/01), one of skill in the art would not be able to carry out the claimed method to produce the intended therapeutic effect without undue experimentation. Thus, even if Applicants could establish that a dopamine replenishment strategy would be expected to result in treatment of the negative symptoms of schizophrenia, the specification does not adequately teach a protocol, as claimed, that could be used to effect the required level of dopamine replenishment. The specification does not disclose what level of dopamine delivery would be therapeutic. It does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the transfected therapeutic cells (and/or protective cells and support cells). Further, the specification does not teach which

combinations of therapeutic cells, protective cells, and support cells would work, nor does it even offer a starting point. The specification discloses a wide variety of cell types that could be used, but does not offer a starting point with regards to a combination of therapeutic cells, protective cells, and support cells that would be effective in treating the negative symptoms of schizophrenia. The skilled artisan is left with the task of testing all these parameters and coming up with a protocol that produces the intended effect. Thus, the skilled artisan would be required to engage in undue experimentation to come up with a protocol that produces the intended effect.

At page 6, paragraph 2 of the response, Applicants point to Watts et al. (2001) and argue that administration of retinal pigment epithelial cells attached to a support matrix to the brain of Parkinson's disease (PD) patients in a phase I/II study resulted in improved motor function in all patients. However, as discussed above, the usefulness of dopamine replenishment in the prefrontal cortex of schizophrenics is unpredictable. Further, the level of dopamine expression required and attainable in PD patients is likely to be different than that required and attainable in schizophrenic patients, given that the etiology of these two diseases is different. Further, given that the etiology of schizophrenia is not well-understood, it is unclear whether the causative process that leads to mesofrontal dopamine deficits will permit adequate replenishment of dopamine in that area of the brain or if it will continually destroy the newly available dopamine, thereby maintaining a dopamine deficit irrespective of the production of dopamine in the region. Given the poor understanding of the etiology of schizophrenia, the fate of dopamine precursors produced in the prefrontal cortex of a diseased brain is unpredictable.

At page 6, paragraph 3 of the response, Applicants argue that the specification teaches administration of a composition comprising cells which produce dopamine or a dopamine precursor to the prefrontal cortex of a patient with schizophrenia and that the composition is administered in an amount

effective to alleviate a negative symptom of schizophrenia. Applicants point to the specification at page 12, lines 1-6 and page 22, lines 12-13. However, as discussed above, the specification does not provide even an initial protocol that produces the intended therapeutic effect. Without a starting point the skilled artisan would not know where to begin or in which direction experimentation should proceed. The amount of composition that would be effective is not known. The specific makeup of a composition (cell type, vector type, if genetically engineered) that would work is not known. Thus, the skilled artisan would be required to engage in undue experimentation, given the limited teachings of the specification.

Given the lack of specific guidance in the instant specification for producing the claimed effect of treating the negative symptoms of schizophrenia, the limited working examples, the unpredictable state of the art with respect to ex vivo gene therapy and cell-based therapies, the broad scope of the claims encompassing the use of any cell type as therapeutic, protective, or support cells, one of skill in the art would have been required to engage in undue experimentation to practice the claimed methods and to make compositions as claimed, useful for the treatment of schizophrenia.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37-40 are indefinite in their recitation of "the cells" because the term has ambiguous antecedent basis. In Claim 37, it is unclear if "the cells" refers to the "therapeutic cells" or the "Sertoli cells" or both. In Claims 38-40, it is unclear if "the cells" refers to the "therapeutic cells," the "protective cells," the "support cells," or all three types of cells.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER